REMARKS

Claims 1-27 were 32-60 are pending and under consideration. Claims 1, 7, 32 and 38 have been amended to clarify that which Applicant regards as the invention. Specifically, claims 1 and 32 have been amended to recite that the first sequences coding for the selectable or detectable marker are not expressed in the transgenic animals prior to the animals being made transgenic. Support for this amendment can be found in the specification, for example, at page 60, lines 11-13. Claims 7 and 38 have been amended to specify only that the first sequences are operably linked to an IRES sequence. Support for this amendment can be found in the specification, for example, at page 15, lines 9-10.

No new matter has been added by these amendments. After entry of the present amendment, claims 1-27 were 32-60 will be pending.

Entry of the foregoing amendments and consideration of these remarks are respectfully requested.

I. Information Disclosure Statement

Applicant acknowledges receipt of the signed and initialed PTO-1449 form.

II. The Rejection Under 35 U.S.C. § 112, First Paragraph For Lack of Enablement Should be Withdrawn

Claims 1-27 and 32-60 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner alleges that the specification is not enabling because (1) there is no expectation of success that a promoter sequence out of physical context of the endogenous gene would provide the same expression pattern as the endogenous gene, and (2) specific disease states are often not associated with a single gene. *See* Office Action, pp. 6-7. Applicant respectfully traverses the rejection.

A. The Specification is Enabling for a Promoter Sequence Out of its Physical Context Providing the Same Expression Pattern as the Endogenous Gene

The Examiner alleges that the specification is not enabling because the specification does not provide evidence that in the context of a transgenic animal that a promoter out of the physical context of the endogenous gene would have the same expression

pattern as the endogenous gene. *See* Office Action, p. 6. The Examiner further cited several references as support in the previous Office Action. *See* Office Action mailed December 31, 2002, pp. 6-9. Applicant respectfully submits that the specification fully enables one of ordinary skill in the art to make and use the invention.

The specification teaches that to obtain expression of the system gene coding sequences in substantially the same pattern as the endogenous characterizing gene large sequences containing all or a portion of the regulatory sequence of a characterizing gene are incorporated into the transgene to regulate the expression of the system gene. *See* the specification, p. 19, ll. 13-18; Pub. App. at ¶ 149[1] and p. 21, ll. 14-16; Pub. App. at ¶ 154. In particular, the specification teaches that the characterizing gene genomic sequences are preferably in a vector that can accommodate such large lengths of sequence, *e.g.*, cosmids, YACs, and BACs that encompass 50 to 300 kb of sequence. *See* the specification, p. 19, ll. 9-14; Pub. App. at ¶ 149. The specification also points out that it is within the knowledge of one of skill in the art to determine the sufficient length of the promoter region required to promote transcription. *See* the specification, p.12, ll. 31-33; Pub. App. at ¶ 122.

The references cited by the Examiner do not teach using large sequences containing all or a portion of the regulatory sequence of a characterizing gene sufficient to direct expression of the system gene coding sequences in substantially the same expression pattern as the endogenous characterizing gene. Eid *et al.* (Dev. Dyn., 1993) teaches that transgenic mice generated with various Hoxb-6 gene promoters operatively linked to LacZ reporter gene could not entirely reproduce the regulation of the endogenous Hoxb-6 gene. *See* Eid *et al.*, Dev. Dyn. 1993, 196:205-216. However, Eid *et al.* suggested that this failure was due to the need for larger genomic regions of the Hoxb cluster. *See* Eid *et al.* at p. 205, Abstract, lines 24-36. Similarly, Sun *et al.* (Biochem. Soc., 2002) teaches that constructs containing only up to 2400 bp of 5' flanking sequence of prosaposin were unable to generate the same expression pattern as the endogenous promoter and that "additional regulatory elements outside 5' of 2400 bp promoter fragment appear to be needed for the physiologic control of the prosaposin locus." Sun *et al.*, Biochem. Soc. 2002, Abstract. The Examiner's characterization of Leinwand *et al.* also shows that to obtain the same expression pattern as the endogenous gene, additional elements of the promoter fragment appear to be necessary. *See* Office Action mailed December 31, 2002, p. 6.

[1] "Pub. App.", as used herein, refers to Published Application US 2003/0051266

All that Eid *et al.*, Sun *et al.*, and Leinwand *et al.* disclose is that an insufficient length of the regulatory sequence of the gene was incorporated into the transgene to mimic the expression pattern of the endogenous gene. The specification teaches that the transgene of the invention should contain all or a portion of the characterizing gene genomic sequence sufficient to direct the expression of the system gene coding sequence to have the same expression pattern of the endogenous characterizing gene. *See* the specification, p. 59, ll. 4-10; Pub. App. at ¶ 178. The specification also provides an example in Section 5 of making and using a BAC vector of the invention.

Applicant respectfully submits work in the transgenic mouse field as demonstrating using large genomic sequences containing all or a significant portion of the gene regulatory region reliably directs the expression of a transgene to have the same or highly similar expression pattern as an endogenous gene. For example, several independent groups achieved position-independent optimal expression in transgenic mice using yeast artificial chromosomes ranging in size from 103 kB to 680 kB. *See, e.g.*, Giraldo et al., 2001, Transgenic Res. 10:83-103 ("Giraldo"; Exhibit A). Numerous genes have been expressed in transgenic mice using BACs in which the transgene is found to have the same expression pattern as the endogenous gene. These include ABCA1 transporter (255 kb BAC clone; Cavelier et al., 2001, J. Biol. Chem. 276:18046-18051; Exhibit B), SM22α, (150 kb BAC clone; Xu et al., 2003, Am. J. Physiol. Heart Circ. Physiol. 284:H1398-H1407; Exhibit C), human β-globin (160 kb BAC clone; Huang et al., 2000, Blood Cells, Molecules, and Diseases 26:598-610; Exhibit D), and human smooth muscle calponin (>100 kb BAC clone; Miano et al., 2002, Am. J. Physiol. Heart Circ. Physiol. 282:H1793-H1803; Exhibit E). These results make it clear that the use of large genomic fragments (>100kb) results in an expression pattern that is independent of the site of integration and that mimics that of the endogenous gene. Thus, contrary to the Examiner's assertion, there is a reasonable expectation of success for a transgene having a promoter out of its physical context of its endogenous gene to have the same expression pattern as the endogenous gene.

Accordingly, the specification provides sufficient guidance to one of ordinary skill in the art to construct a transgene of the invention and determine whether the characterizing gene regulates the expression of the system gene to be substantially the same as the endogenous characterizing gene.

For the reasons stated above, Applicant respectfully requests that the rejection of claims 1-27 and 32-60 based on 35 U.S.C. § 112, first paragraph be withdrawn.

B. The Specification is Enabling for Genes Associated with Specific Diseases

The Examiner alleges that the specification fails to enable dependent claims that recite specific pathways and specific phenotypes with which characterizing genes are associated with because the specification does not teach specific genes that are responsible for producing specific phenotypes and the specification does not provide description of these genes or means to isolate and use these genes within the context of the claims. *See* Office Action, p. 7. Applicant respectfully disagrees.

Dependent claims reciting specific pathways (*e.g.*, claim 17) require that each of the endogenous genes endogenously express a protein product that is part of a recited pathway. Representative genes associated with these pathways are disclosed, *e.g.*, in Tables 1-15 which lists their Genebank/Unigene Accession Number or MGI Database Accession Number. *See* the specification, pp. 23-57; Pub. App ¶¶ 160-174. The specification further teaches that one may obtain regulatory sequences of these endogenous genes sufficient to direct the expression of a system gene coding sequence to have the same expression pattern of the endogenous gene from, *e.g.*, BAC genomic libraries. *See* the specification at p. 59, l. 31 to p. 60, l. 2; Pub. App ¶ 180. Using the methods disclosed in the specification and known in the art, one can further manipulate the desired BAC clone as needed. Thus, the specification is fully enabling for genes associated with specific pathways.

Dependent claims reciting specific disease states (*e.g.*, claim 21) specify that the endogenous genes are implicated in certain neurological or psychiatric diseases. To be implicated in a disease, a gene product has only to be involved in some way, for example aberrant expression of the gene product or expression of a mutant gene product causes, contributes to or is at least correlated with onset and/or progression of a disease. Many, if not all, of the genes listed in Tables 1-15 are known in the art to be implicated in the diseases specified in the claims. To provide but a few examples, dopamine gene expression has been associated with schizophrenia (*See* Schmauss *et al.*, Proc. Natl. Acad. Sci. USA 1993, 90:8942-8946; Exhibit F) and attention-deficit hyperactivity disorder (*See* DiMaio *et al.*, J. Psychiatry Neurosci. 2003, 28:27-38; Exhibit G) and serotonin receptor 1A has been associated with anxiety-related disorder (*See* Ramboz *et al.*, Proc. Natl. Acad. Sci. USA 1998, 95:14476-14481; Exhibit H). Since the genes are known, one could screen BAC libraries to obtain clones with sufficient regulatory sequences and produce the appropriate transgenes, as described above. Thus, given the specification and knowledge of one of

ordinary skill in the art, one could produce a collection of transgenic animals which endogenous genes express a protein product implicated in the recited diseases.

For the reasons stated above, Applicant submits that the rejection of claims 1-27 and 32-60 under 35 U.S.C. § 112, first paragraph is overcome, and respectfully request that that the rejection be withdrawn.

III. Claims 1-27 and 32-60 are Definite Under 35 U.S.C. § 112, Second Paragraph

Claims 1-27 and 32-60 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Examiner has maintained that the recitation of "substantially the same expression pattern" in Claims 1 and 32 is indefinite because the metes and bounds of the phrase is not clearly defined. Specifically, the Examiner states that the definition fails to clearly indicate if other cells not normally expressing the endogenous gene may also express the transgene. The Examiner queries whether a transgenic animal in which all the cells express the transgene under a more promiscuous promoter would anticipate the claims. The Examiner alleges that the definition implies that expression of the endogenous gene must be detectable by *in situ* hybridization and it is unclear where the transgene expression pattern is present in 100% of the cells normally expressing the endogenous gene but can not be detected by *in situ* hybridization would anticipate the claims. The Examiner further alleges that there is no context for what is encompassed by the term "pattern" with respect to any aspect of regulated expression times or levels of expression in the cell. Applicant respectfully disagrees.

Applicant respectfully submits that expression of the transgene in cells not normally expressing the endogenous gene would defeat the purpose of the invention and is clearly not contemplated by the present invention. The specification clearly states that "the system gene coding sequence is expressed in substantially the same expression pattern as the endogenous characterizing gene in the transgenic animal or at least in the anatomical region or tissue of the animal . . . containing the population of cells to be marked by expression of the system gene coding sequences *so that tissue can be dissected from the transgenic mouse which contains only cells of interest expressing the system gene coding sequences.*" Specification, p. 13, ll. 26-33; Pub. App ¶ 125, emphasis added. Thus, the expression pattern would not include expression of the transgene in cells not normally expressing the endogenous gene. One of ordinary skill in the art reading the specification, especially the definition of "substantially the same expression pattern" in view of the text immediately

preceding it, would understand that cells not expressing the endogenous gene would not express the transgene. Furthermore, what is meant by "expression pattern", as indicated by the definition of "substantially the same expression pattern" and the preceding text, is that the gene is expressed in the same population of cells as the endogenous gene. A transgene that is expressed in cells that normally do not express the endogenous gene would not have the same expression pattern as the endogenous gene. Therefore, the specification clearly sets forth the metes and bounds of "substantially the same expression pattern" in claims 1 and 32.

Furthermore, the definition of "substantially the same expression pattern" implies that expression of both the transgene and the endogenous gene must be detectable by *in situ* hybridization. The definition of "substantially the same expression pattern" goes on to recite "[b]ecause detection of the system gene expression product may be more sensitive than in situ hybridization detection of the endogenous characterizing gene messenger RNA, ...". This means that expression of both the transgene and the endogenous gene must be detectable by *in situ* hybridization to control for any differences in sensitivity of detection.

Finally, as discussed above, the context of the term "pattern" is provided by the definition. The expression pattern refers to the expression of the gene product in the same populations of cells as the endogenous gene. There is no requirement for expression times of levels of expression in cells.

The Examiner also maintains that claims 7 and 38 are indefinite because the functional relationship of the IRES to the other sequences is not clearly set forth. The Examiner alleges that the characterizing gene could be either the endogenous gene or the transgene. Applicant respectfully disagrees.

Claims 7 and 38, as amended, are directed to collections of two or more transgenic animal lines comprising transgenes and methods of making such collections wherein the transgene comprises (a) first sequences coding for a selectable or detectable marker protein that is operably linked to an IRES sequence, and (b) regulatory sequences of a characterizing gene corresponding to an endogenous gene or ortholog of an endogenous gene operably linked to said first sequences. In certain embodiments, claims 7 and 38 are directed to the situation where a system gene encoding the marker protein (1) has its own IRES sequence and (2) is inserted in the 3' untranslated region of the characterizing gene (*See* the specification, p. 14, ll. 20-25; Pub. App ¶ 128) or into a separate cistron in the 5' region of the characterizing gene (*See* the specification, p. 15, ll. 6-8; 130). In other words, the IRES directs expression of the system gene, *e.g.*, if embedded in the untranslated region of the characterizing gene sequences. As noted in the specification, at p. 15, ll. 10-14; Pub. App ¶

131, the use of an IRES can direct expression of a particular coding sequence in a polycistronic mRNA in which multiple gene sequences are under the control of the characterizing gene regulatory sequences. In either situation described above, the first sequences, *i.e.*, the system gene, is operably linked to an IRES sequence, which directs translation of the system gene product, and the regulatory sequences of the characterizing gene which directs transcription of the system gene sequences (and perhaps other sequences if in the context of a polycistronic mRNA). Therefore, claims 7 and 38 are clear and definite.

For the reasons stated above, claims 1-27 and 32-60 are definite under 35 U.S.C. § 112, second paragraph and the rejection should be withdrawn.

IV. Claims 1, 2, 14, 18, 19, 22, 32, 33, 45, 49, 50, 53, 56, and 60 are patentable over U.S. Patent No. 6,353,151

Claims 1, 2, 14, 18, 19, 22, 32, 33, 45, 49, 50, 53, 60, and 60 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,353,151 to Leinwand *et al.* ("Leinwand"). Applicant respectfully disagrees.

Claims 1 and 32, as amended, disclose a collection of two or more lines of transgenic animals and methods of making such collections wherein each transgenic animal comprises a transgene comprising first sequences coding for a selectable or detectable marker protein operably linked to regulatory sequences of a characterizing gene corresponding to an endogenous gene or ortholog of an endogenous gene so that the expression pattern of the first sequence is substantially the same as the expression pattern of the endogenous characterizing gene wherein the characterizing gene is different for each of said transgenic animals and wherein said first sequences are not expressed in said transgenic animals prior to the animals being made transgenic. In other words, claims 1 and 32, as amended, are directed at collections of two or more animal lines where each line has a system gene regulated by the regulatory sequences of a different characterizing gene and the system gene is not expressed in non-transgenic animals expressing the characterizing gene.

In contrast, Leinwand only discloses use of different regulatory sequences, *i.e.*, rat and mouse heart tissue specific promoters, of a single characterizing gene, *i.e.*, α myosin heavy chain. The claims require that the characterizing gene itself, as opposed to the regulatory sequence of the characterizing gene, be different for each of the transgenic animals. A characterizing gene sequence encompasses the endogenous sequence as well as its orthologs, *i.e.*, the corresponding sequences derived from different species. See the

specification, p. 12, ll. 2-5; Pub. App ¶ 121. Thus, rat and mouse α heavy chain promoters would not be directed to two different characterizing genes.

While Leinwand also discloses another promoter, *i.e.*, a myosin light chain 2V promoter (*see* Leinwand, col. 8), it is clear that the use of other promoters are alternative embodiments. Leinwand does not teach or suggest a collection of transgenic animals. As claimed in claim 1, Leinwand provides for a transgenic mouse having a heart tissue-specific promoter selected from the group consisting of mouse and rat α heavy chain promoters. Leinwand does not teach or suggest producing a collection of two transgenic mice wherein one has a transgene with a mouse α heavy chain promoter and one has a rat α heavy chain promoter, much less a collection of transgenic mice wherein one has a myosin light chain 2V promoter and one has a α heavy chain promoter. The Examiner cited Example 1 as support for the assertion that five independent lines of mice were reduced to practice. See Leinwald, Example 1. However, all five transgenic mouse lines were generated from a single transgene containing 3.3 kb of rat α myosin heavy chain 5' flanking DNA. Thus, a collection of transgenic animals wherein each line has a system gene regulated by the regulatory sequences of a different characterizing gene is not provided.

Moreover, Leinwald, in Example 1, demonstrates that expression of the transgene was expressed only in the heart, while expression of the endogenous gene was seen in both the heart and lung. Thus, the expression pattern of the transgene is not substantially the same as the expression pattern of the endogenous gene. In fact, the Examiner citers to Leinwald on page 6 of the Office Action to support the contention that transgene expression in transgenic mice is unreliable, indicating that, in Leinwald, only a generalized expression pattern was obtained and that additional promoter elements appeared to be necessary to obtain the same expression pattern as the endogenous gene. Thus, Leinwald does not teach each and every element of the presently claimed invention.

Futhermore, in Leinwald, the characterizing gene, i.e., α myosin heavy chain, is the same as the system gene and is endogenously expressed in similar mice that are not transgenic. Claim 1 and 33 require that the first sequences, i.e., the system genes, are not expressed in the transgenic animals prior to the animals being made transgenic. Clearly, α myosin heavy chain is also expressed in the animals prior to their being made transgenic. Thus, Leinwald does not teach each and every element of the presently claimed invention.

Claims 2, 14, 18, 19, and 22, which are dependent on claim 1, and claims 33, 45, 49, 50, 53, 56, and 60, which are dependent on claim 32, are also directed to collections

of lines of transgenic animals and methods of making such collections, therefore Leinwand also does not anticipate these claims.

For the reasons stated above, Leinwand does not disclose each and every limitation of the claimed invention and does not anticipate Applicant's present invention. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 102(e) of claims 1, 2, 14, 18, 19, 22, 32, 33, 45, 49, 50, 53, 56, and 60 be withdrawn.

V. The Rejection for Double Patenting is a Provisional Rejection

Claims 1-27 and 32-60 stand provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-27 and 32-60 of co-pending Application No. 10/077,025. Since this is a provisional rejection, upon indication of allowable subject matter in the instant application or co-pending Application No. 10/077,025, Applicant will cancel or amend the conflicting claims so that they are no longer coextensive in scope.

CONCLUSION

It is believed that no fee is due in connection with this amendment (other than for the Extension of Time and the Notice of Appeal submitted separately herewith). However, should the Patent Office determine that a fee is due, please charged the required amount to Jones Day Deposit Account No. 50-3013.

Applicant submits that the entire application is now in condition for allowance, early notice of which would be appreciated. The Examiner is invited to telephone the undersigned should any issues remain.

Respectfully submitted,

Dated: March 24, 2004

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Enclosures